

PATENT COOPERATION TREATY

PCT



Translation

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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|---|---|---|
| Applicant's or agent's file reference C37295PC | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
| International application No. PCT/EP2003/002487 | International filing date (<i>day/month/year</i>) 11 March 2003 (11.03.2003) | Priority date (<i>day/month/year</i>) 11 March 2002 (11.03.2002) |
| International Patent Classification (IPC) or national classification and IPC C07K 5/06 | | |
| Applicant CURACYTE AG | | |

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|--|--|
| <p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <u>7</u> sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of <u>9</u> sheets.</p> | |
| <p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the report</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p>IV <input type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input type="checkbox"/> Certain observations on the international application</p> | |

| | |
|---|---|
| Date of submission of the demand 29 July 2003 (29.07.2003) | Date of completion of this report 24 May 2004 (24.05.2004) |
| Name and mailing address of the IPEA/EP | Authorized officer |
| Facsimile No. | Telephone No. |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/EP2003/002487

I. Basis of the report

1. With regard to the elements of the international application:*

- ☐ the international application as originally filed
- ☒ the description:
pages _____ 1-31 _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____
- ☒ the claims:
pages _____, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages _____ 1-15 _____, filed with the letter of _____ 08 April 2004 (08.04.2004)
- ☐ the drawings:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____
- ☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/fig _____

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International Application No.

PCT/EP2003/002487

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 14-15

because:

☒ the said international application, or the said claims Nos. 14-15
relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

I. Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments)*:

I.5

1. Thirteen claims, which are to replace all the preceding claims, were submitted with the letter of 7 April 2004.

The following amendments to the original set of claims were made in the new claim 1:

i) The parameter P2 was replaced by the definition in the original claims 5 and 6.

ii) The alternative "3-guanidinomethyl phenylalanine" in the original claim 5 was replaced by "D-3-guanidinomethyl phenylalanine".

iii) The specific products in example 4, Nos. 1, 2, 10, 13, 19, 20, 22, 23, 27 and 30 were incorporated as additional alternatives in the new claim 1.

iv) The characterizing portion of the original claim 1, namely the restriction "one or more charged radicals ... are present in the radicals R1, R2, R3 or R5" was deleted.

Following omission of the restriction in item iv), alternatives in which no single radical R1, R2, R3 or R5 is a "charged radical" are now also claimed. An alternative of this kind is exemplified by the following combination: R1 = R2 = R3 = hydrogen and R5 = aryl. This group constitutes an unallowable broadening of the scope of protection (PCT Rule 34(2)(b)). Pursuant to PCT Rule 70.2(c), the international preliminary examination report is established as if the amendment had not been made.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/E 8/02487

I. Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments);*

This legal consequence was already mentioned in the official communication of 12 February 2004 in response to the amendments, to which objection was also raised under PCT Rule 34(2)(b).

The international preliminary examination report was therefore established on the basis of the original claims 1-15, which are denoted as "original" on the PCT Form. All the statements in this report therefore refer to the claims originally filed.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/E 3/02487

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III.1

**Non-establishment of opinion with regard to novelty,
inventive step and industrial applicability**

1. Claims 14 and 15 relate to subject matter which this Authority considers to fall under PCT Rule 67.1(iv). Consequently, no opinion is established with regard to the industrial applicability of the subject matter of these claims (PCT Article 34(4)(a)(i)).

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/03/02487

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. Statement**

| | | | |
|-------------------------------|--------|---------------------------------|-----|
| Novelty (N) | Claims | 7 (as originally filed) | YES |
| | Claims | 1-6, 8-15 (as originally filed) | NO |
| Inventive step (IS) | Claims | | YES |
| | Claims | 1-15 (as originally filed) | NO |
| Industrial applicability (IA) | Claims | 1-13 (as originally filed) | YES |
| | Claims | | NO |

2. Citations and explanations

1. Reference is made to the following international search report citations:

D1: HO J Z ET AL: BIOORG. MED. CHEM. LET. &
XP002245018

D2: WO-A-01/96366

D3: WO-A-00/58346

D4: US-A-6 030 972

D5: US-A-5 726 159

D6: WO-A-94/29336

D7: KUENZEL S ET AL: BIOORG. MED. CHEM. LET. &
XP002245019.

2. The factor Xa inhibitors disclosed in D1 (see compounds 1 and 2g) differ from the dipeptide derivatives as per the application in that a hydroxyl group regarded as a "charged group" is located on the heterocyclic ring and therefore does not fall under the characterizing portion of claim 1, which claims a "charged group" in at least one of the radicals R₁, R₂, R₃ and R₅.

A generic range of overlap exists between the products of claims 1-5 of D2 and the subject matter

of the invention. The structurally closest compound is the product in example 2, wherein R_4 stands for $BzSO_2$ and R_3 stands for CH_2OH . Although the hydroxyl group is considered to be a "charged" group with respect to the isosteric amino group, it is not located on the position of the claimed radicals R_1 , R_2 , R_3 or R_5 .

Numerous specific products from the range of overlap between the products of claim 1 of D3 and the subject matter of the invention which fall under the definition of claims 1-6 and 8-10 are disclosed (see the tables on pages 34 to 41, for example product Nos. 5, 8, 9, 11, 15, 18-20, 23, 26, 28-29, 31, 33, 35-39). Since D3 further discloses the use as anticoagulants (see page 42, line 23) and claims medicaments and drugs for said use, and the production is carried out using amidinobenzylamines containing protected acyl groups, claims 1-6 and 8-15 do not appear to have satisfied the requirements of PCT Article 33(2) in relation to D3.

A range of overlap also exists between the subject matter of the application and D4, D5 and D6.

The products in tables 2 and 3 of D7 fall within the claimed range; moreover, the claimed use (figure 1) and the production (see synthesis of compound 23 on page 647) of the products are disclosed.

Consequently, the subject matter of claims 1-6 and 8-15 does not appear to have satisfied the requirements of PCT Article 33(2) in relation to D7.

3. Inventive step:

The applicant has addressed the problem of providing an active substance suitable for factor Xa applications, which, in addition to high activity and selectivity, exhibits high retention in the body (see

page 3). The effects reported in examples 2 and 3, indicate that this problem was solved by means of the features of the characterizing portion of claim 1, namely the presence of at least one "charged" group in the radicals R_1 , R_2 , R_3 or R_5 . In view of the fact that products as per the solution which have factor Xa activity are known, the structural basic motif of a modified dipeptide which has a D-configuration in the P2 unit and which contains, in addition to the known terminal amidino or guanidino group, an additional "charged group", is not considered to be inventive. Consequently, that subject matter, which can be regarded as novel, does not appear to involve an inventive step. The claims do not appear to have satisfied the requirements of PCT Article 33(3).

Curacyte AG
PCT/EP03/02487

January 30, 2004
C37295PC BÖ/AT

New Claims

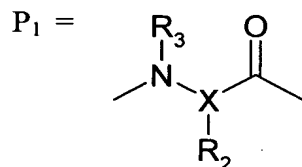
1. A compound of the formula I



where

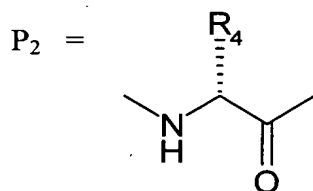
A is P_2-P_1 with

10



and

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;

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R_1 is H or $-(CH_2)_aCOOR_6$ with $a = 0, 1, 2, 3, 4$ or 5 , preferably with $a = 0, 1$ or 2 , where R_6 is a branched or unbranched alkyl radical having preferably 1 to 6 C atoms, in particular 1 to 3 C atoms, especially ethyl;

25

R_2 is $-(CH_2)_cCOOR_8$ with $c = 1, 2, 3$ or 4 , where R_8 is H or a branched or unbranched alkyl radical having preferably 1 to 6 C atoms, in particular 1 to 3 C atoms, especially ethyl, or

$-(CH_2)_e$ -guanidino, $-(CH_2)_e$ -imidazole or $-(CH_2)_eNHR_{10}$ with $e = 1, 2, 3, 4$ or 5 ,

30

where R_{10} is H, a branched or unbranched alkyl radical having 1-16, in

particular 1-8, especially 1-3, C atoms or a substituted or unsubstituted aryl, heteroaryl, aralkyl or heteroaralkyl radical, where the alkyl radical preferably has 1 to 16, in particular 1 to 8, especially 1 to 3, C atoms, and the aryl or heteroaryl radical preferably has 4 to 14, in particular 6 to 10, especially 6, C atoms and preferably 1 to 3 N as heteroatom; und

R_4 is a branched or unbranched alkyl radical having 1 to 8, preferably 1 to 3, C atoms, $-(CH_2)_fOR_{11}$, $-(CH_2)_fSR_{11}$, $-(CH_2)_f$ guanidino, $-(CH_2)_f$ imidazole, $-(CH_2)_fR_{11}$ or $-(CH_2)_fNHR_{11}$ with $f = 1, 2, 3, 4$ or 5 , preferably 1 or 2, in particular 1, where R_{11} is a branched or unbranched alkyl radical having 1 to 16, preferably 1 to 8, in particular 1-4 C atoms, especially tbutyl or a substituted or unsubstituted aryl, heteroaryl, aralkyl or heteroaralkyl radical, where the alkyl radical preferably has 1 to 16, in particular 1 to 8, especially 1 to 3, C atoms, and the aryl or heteroaryl radical preferably has 4 to 14, in particular 6 to 10, especially 6, C atoms and preferably 1 to 3 N as heteroatom; where P_2 in the structure A of the formula I is in the D configuration;

or

R_2 is an H; and

R_4 is $-(CH_2)_f$ guanidino, $-(CH_2)_f$ imidazole or $-(CH_2)_fR_{11}$ with $f = 1, 2, 3, 4$ or 5 , preferably 1 or 2, in particular 1, where R_{11} is a substituted or unsubstituted aryl or heteroaryl radical which preferably has 4 to 14, in particular 6 to 10, especially 6, C atoms and preferably 1 to 3 N as heteroatom; where P_2 in the structure A of the formula I is in the D configuration;

or

R_2 is a branched or unbranched alkyl radical having 1 to 8 C atoms, preferably having 1 to 3 C atoms, or $-(CH_2)_d-OR_9$ with $d = 1, 2, 3$ or 4 , where R_9 is H, or $-(CH_2)_eOR_{10}$ or $-(CH_2)_eSR_{10}$, with $e = 1, 2, 3, 4$ where R_9 is H, or $-(CH_2)_eOR_{10}$ or $-(CH_2)_eSR_{10}$, with $e = 1, 2, 3, 4$ or 5 , where R_{10} is H, a branched or unbranched alkyl radical having 1-16, in particular 1-8, especially 1-3, C atoms or a substituted or unsubstituted aryl, heteroaryl, aral-

kyl or heteroaralkyl radical, where the alkyl radical preferably has 1 to 16, in particular 1 to 8, especially 1 to 3, C atoms, and the aryl or heteroaryl radical preferably has 4 to 14, in particular 6 to 10, especially 6, C atoms and preferably 1 to 3 N as heteroatom; and

5 R_4 is $-(CH_2)_f$ -guanidino, $-(CH_2)_f$ -imidazole or $-(CH_2)_f-R_{11}$ with $f = 1, 2, 3, 4$ or 5, preferably 1 or 2, in particular 1, where R_{11} is a substituted or unsubstituted or heteroaryl radical which preferably has 4 to 14, in particular 6 to 10, especially 6, C atoms and preferably 1 to 3 N as heteroatom; where P2 in the structure A of the formula I is in the D configuration;

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R_3 is H or $-(CH_2)_bR_7$ with $b = 1, 2, 3, 4, 5, 6, 7$ or 8, preferably with $b = 2$ or 3, where R_7 is H, a branched or unbranched alkyl radical having 1 to 10 C atoms, preferably having 1 to 3 C atoms, or a charged radical, preferably a $-(CH_2)_jCOOR_{13}$, $-(CH_2)_jSO_2R_{13}$, $-(CH_2)_jNH_2$, $-(CH_2)_j$ -amidino, 15 $-(CH_2)_j$ -hydroxyamidino or $-(CH_2)_j$ -guanidino group with $j = 0, 1$ or 2, where R_{13} is H or an alkyl radical having preferably 1 to 6 C atoms, in particular 1 to 4, especially ethyl;

20 R_5 is $-SO_2R_{12}$, where R_{12} is a substituted or unsubstituted aralkyl or heteroaralkyl radical, preferably benzyl,

where R_5 may be modified with a charged or uncharged group, preferably a $-(CH_2)_jCOOR_{13}$, $-(CH_2)_jSO_2R_{13}$, $-(CH_2)_jNH_2$, $-(CH_2)_j$ -amidino, $-(CH_2)_j$ -hydroxyamidino or $-(CH_2)_j$ -guanidino group with $j = 0, 1$ or 2, where R_{13} is H or an alkyl radical having preferably 1 to 6 C atoms, in particular 1 to 4, especially ethyl;

25

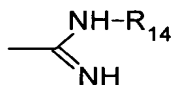
U is a phenyl or cyclohexyl radical;
a heterophenyl or heterocyclohexyl radical having preferably at least one N, S or O as heteroatom, in particular pyridine, piperidine or pyrimidine, 30 or
is a thiophene radical;

V is $(\text{CH}_2)_n$ with $n = 0, 1, 2$ or 3 , preferably 0 ;

X is N or CH, preferably CH;

Y is N or $(\text{CH})_m$ with $m = 0$ or 1 , preferably CH;

Z occurs in the 3 or 4 position and is an aminomethyl, a guanidino function or an amidino group



where R_{14} is H, OH, NH_2 , $-\text{COR}_{15}$ or $-\text{COOR}_{15}$, where R_{15} is a branched or unbranched alkyl radical having 1 to 16, preferably 1 to 8, in particular 1 to 4, especially 1 to 2, C atoms or a substituted or unsubstituted aryl or heteroaryl, aralkyl or heteroaralkyl radical, where the alkyl radical preferably has 1 to 16, in particular 1 to 8, especially 1 to 4 and particularly preferably 1 to 2, C atoms and the aryl or heteroaryl radical preferably has 4 to 14, in particular 6 to 10, especially 6, C atoms and preferably 1 to 3 N as heteroatom;

characterized in that one or more charged radicals preferably derived from $-\text{COOH}$, $-\text{CH}(\text{COOH})_2$, $-\text{SO}_2\text{H}$, NH_2 , an amidino, hydroxyamidino, amidrazono or guanidino group are present in the radicals R_1 , R_2 , R_3 or R_5 ;

or a compound of the formula I in the form of a prodrug or in the form of its salt.

2. The compound as claimed in claim 1, where U is substituted at 1, 2 or 3 positions preferably by a halogen, in particular fluorine or chlorine, or a methyl, ethyl, propyl, methoxy, ethoxy or propoxy radical.
3. The compound as claimed in claim 1 or 2, where a carboxyl group is present protected as ester, preferably as ethyl ester, and is converted into a carboxyl group in the manner of a prodrug only after intake in the body.

4. The compound as claimed in at least one of claims 1 to 3, where R₉ in this case is an alkylcarbonyl, aralkylcarbonyl, alkyloxycarbonyl or aralkyloxycarbonyl radical, where the alkyl radical preferably has 1 to 6, in particular 1 to 4, C atoms and the aryl radical preferably has 5 to 8, in particular 6, C atoms; and where R₉ is converted into a carboxyl group in the manner of a prodrug only after intake in the body.
5. The compound as claimed in at least one of claims 1 to 4, characterized in that P₂ in structure A of the formula I is derived from one of the following amino acids in the D configuration: D-2,3-diaminopropionic acid, D-2,4-diaminobutyric acid, D-ornithine, D-citrulline, D-homocitrulline, D-norcitrulline, D-arginine, D-homoarginine, D-norarginine, D-4-guanidinophenylalanine, D-4-guanidinophenylhomoalanine, D-4-guanidinophenylglycine, D-3-guanidinophenylalanine, D-3-guanidinophenylhomoalanine, D-3-guanidinophenylglycine, D-4-amidinophenylalanine, D-4-amidinophenylhomoalanine, D-4-amidinophenylglycine, D-3-amidinophenylalanine, D-3-amidinophenylhomoalanine, D-3-amidinophenylglycine, D-4-aminomethylphenylalanine, D-4-aminomethylphenylhomoalanine, D-4-aminomethylphenylglycine, D-3-aminomethylphenylalanine, D-3-aminomethylphenylhomoalanine, D-3-aminomethylphenylglycine, D-4-guanidinomethylphenylalanine, D-4-guanidinomethylphenylhomoalanine, D-4-guanidinomethylphenylglycine, D-3-guanidinomethylphenylalanine, D-3-guanidinomethylphenylhomoalanine, D-3-guanidinomethylphenylglycine, D-4-piperidinylalanine, D-4-piperidinylhomoalanine, D-4-piperidinylglycine, D-4-N-(amidino)piperidinylalanine, D-4-N-(amidino)piperidinylhomoalanine, D-4-N-(amidino)piperidinylglycine, D-3-piperidinylalanine, D-3-piperidinylhomoalanine, D-3-piperidinylglycine, D-3-amidinopiperidinylalanine, D-3-amidinopiperidinylhomoalanine, D-3-amidinopiperidinylglycine, D-4-aminocyclohexylalanine in cis or trans, D-4-aminocyclohexylhomoalanine in cis or trans, D-4-aminocyclohexylglycine in cis or trans, n-butylamidinoglycine, n-pentylamidinoglycine, n-

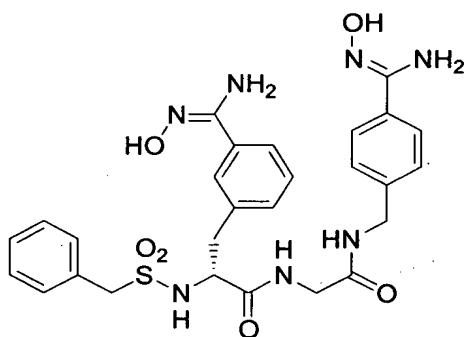
propylamidinoglycine, D-alanine(3-(1-N-piperazinyl) or D-homoalanine(3-(1-N-piperazinyl).

6. The compound as claimed in at least one of claims 1 to 4, characterized in that P₂ in the structure A of the formula I is derived from one of the following amino acids in the D configuration: D-canavanine, D-homocanavanine, D-norcanavanine, 2-amino-4-amidinohydrazonobutyric acid, 2-amino-3-amidinohydrazonopropionic acid, 2-amino-5-amidinohydrazonopentanoic acid, 2-amino-4-(pyridin-4-ylamino)butyric acid, 2-amino-4-(pyridin-4-ylamino)propionic acid, 2-amino-4-(pyridin-4-ylamino)pentanoic acid, 4-imidazolylpropargylglycine, D-histidine, D-homohistidine, D-histidine-(1-methyl), D-homohistidine-(1-methyl), D-histidine-(3-methyl), D-homohistidine-(3-methyl), D-alanine(4-[5-2(-amino)imidazolyl], D-homoalanine(4-[5-2(-amino)imidazolyl], D-glycine(4-[5-2(-amino)imidazolyl], D-alanine(4-pyridyl), D-homoalanine(4-pyridyl), D-glycine(4-pyridyl), D-alanine(3-pyridyl), D-homoalanine(3-pyridyl), D-glycine(3-pyridyl), D-alanine(2-pyridyl), D-homoalanine(2-pyridyl), D-glycine(2-pyridyl), D-alanine(3-(2-pyrimidinyl), D-homoalanine(3-(2-pyrimidinyl), D-alanine(3-(5-pyrimidinyl), D-homoalanine(3-(5-pyrimidinyl), D-2-amino-3-(2-aminopyrimidin-5-yl)propionic acid, D-2-amino-4-(2-aminopyrimidin-5-yl)butyric acid, D-alanine(3-(2-benzimidazolyl)), D-homoalanine(3-(2-benzimidazolyl)), D-alanine(3-(3-quinoliny)), D-homoalanine(3-(3-quinoliny)), D-tryptophan, D-homotryptophan, D-tryptophan substituted by aminoalkyl groups on the indole ring, D-homotryptophan substituted by aminoalkyl groups on the indole ring, D-2-amino-3-(6-aminopyridin-3-yl)propionic acid, D-2-amino-4-(6-aminopyridin-3-yl)butyric acid, D-2-amino-3-(6-amino-2-methylpyridin-3-yl)propionic acid, D-2-amino-4-(6-amino-2-methylpyridin-3-yl)butyric acid, D-2-amino-3-(6-amino-2,4-dimethylpyridin-3-yl)propionic acid, D-2-amino-4-(6-amino-2,4-dimethylpyridin-3-yl)butyric acid, D-4-hydroxyamidinophenylalanine, D-4-hydroxyamidinophenylhomoalanine, D-4-hydroxyamidinophenylglycine, D-3-hydroxyamidinophenylalanine, D-3-hydroxyamidinophenyl-

homoalanine, D-3-hydroxyamidinophenylglycine, D-4-aminophenylalanine,
D-4-aminophenylhomoalanine, D-4-aminophenylglycine, D-3-
aminophenylalanine, D-3-aminophenylhomoalanine, D-3-
aminophenylglycine.

5

7. A compound of the formula I, characterized in that the compound has the following structure:



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where the hydroxyamidino groups present in the structure are converted into the analogous amidino groups in the manner of a prodrug only after intake in the body, resulting in the inhibitor structure with inhibitory activity.

- 15 8. The compound as claimed in at least one of claims 1 to 7, characterized in that the substituent on the substituted aryl, heteroaryl, aralkyl or heteroaralkyl radical is a halogen, preferably fluorine, chlorine or bromine, in particular fluorine or chlorine.
- 20 9. The compound as claimed in at least one of claims 1 to 8, characterized in that the compounds are preferably in the form of salts, preferably with mineral acids, preferably as hydrochlorides, or preferably as salts with suitable organic acids.

10. The compound as claimed in claim 9, characterized in that preferred salts of mineral acids are also sulfates, and suitable organic acids are, for example, acetic acid, formic acid, methanesulfonic acid, succinic acid, malic acid or trifluoroacetic acid, with preferred salts of organic acids being acetates.

5

11. A method for preparing a compound as claimed in at least one of claims 1 to 10, characterized in that the appropriate amino acids are coupled sequentially onto a 4-acetyloxamidinobenzylamine, with the N-terminal amino acid either already carrying the R₅ radical or the latter subsequently being linked thereto.

10

12. A medicament comprising a compound as claimed in at least one of claims 1 to 10 and pharmaceutically suitable excipients and/or additives.

15

13. The medicament as claimed in claim 12, where the medicament is employed in the form of a tablet, of a coated tablet, of a capsule, of a pellet, suppository, of a solution, in particular of a solution for injection or infusion, of eyedrops, nose and eardrops, of a syrup, of a capsule, of an emulsion or suspension, of a pessary, stick, aerosol, dusting powder, of a paste, cream or ointment.

20

14. The use of a compound as claimed in at least one of claims 1 to 10 or of a medicament as claimed in either of claims 12 or 13 for the therapy or prophylaxis of a cardiovascular disorder or of a thromboembolic event, in particular in oral, subcutaneous, intravenous or transdermal form.

25

15. The use of a compound as claimed in at least one of claims 1 to 10 or of a medicament as claimed in either of claims 12 or 13 for the diagnosis of a thromboembolic event.